

A randomised, double-blind, parallel group study to compare subcutaneous interferon alpha-2a plus podophyllin with placebo plus podophyllin in the treatment of primary condylomata acuminata

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Abstract

Objectives—The primary objective was to determine if six weeks treatment with subcutaneous interferon alpha-2a (IFN) and podophyllin 25% W/V administered twice per week, preceded by IFN alpha-2a three times weekly for one week showed a greater complete response rate in patients with primary condylomata acuminata when assessed at week 10 than treatment with podophyllin and placebo injections in the same schedule. The secondary objective was to compare recurrence rates in complete responders at six months in the two treatment groups.

Design—Randomised, double-blind parallel group study.

Setting—Multicentre study in six genitourinary clinics within the U.K.

Patients—One hundred and twenty-four patients with primary anogenital warts.

Main Outcome Measures—Complete response rate at week 10, and recurrence rate at week 26 in complete responders.

Results—At week 10 analysis of the efficacy population showed complete response in 36% (15/42 patients) of IFN-treated group and 26% (11/43 patients) in the placebo group (no significant difference). Analysis of the safety population at week 26 showed persistence of the complete response in 57% (8/14 patients) of the IFN-treated group and 80% (12/15 patients) of the placebo group (no significant difference). Adverse effects were more common in IFN-treated patients, involved particularly application site reaction and malaise but were generally mild.

Conclusions—At the dose and with the regime described treatment with IFN alpha-2a in combination with podophyllin is no more effective in the treatment of primary anogenital warts than podophyllin alone and is associated with more adverse events.

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Introduction

Podophyllin resin remains one of the most common first line agents in the treatment of anogenital condylomata¹ despite the problems of incomplete response and frequent recur-

rence. Currently available chemical and physical ablative methods aim to remove clinically visible condylomata. Apparently normal epithelium may harbour latent human papillomavirus (HPV) infection which may be responsible for the high incidence of recurrent disease. The known antiviral and immunomodulatory properties of interferons make these agents a theoretically attractive systemic adjuvant treatment in conjunction with standard ablative procedures to treat such latent infection. Interferon treatment involves considerable expense and is associated with characteristic adverse effects and accordingly an improved response rate in combination with cheaper and more practical first line alternatives should be demonstrated before more widespread use could be recommended. The current study was designed with the primary objective of comparing the efficacy of combination treatment with podophyllin and systemic interferon alpha-2a (IFN) versus podophyllin and placebo for the treatment of primary anogenital condylomata and secondly to compare recurrence rates in the two treatment groups over a six month follow-up period.

Patients and methods

This study was conducted in six genitourinary clinics within the United Kingdom after study approval was obtained from each local medical ethics committee.

Patient selection

Patients aged 18-65 years of age with clinically visible condylomata acuminata of the external genitalia and/or perianal area for less than six months with no history of previous treatment were eligible for study entry. Patients had to give witnessed oral or written informed consent, be able and willing to conform with the requirements of the study and be HIV antibody negative. Patients were excluded if they had internal genital or anal canal lesions only, had any single lesion more than 3 cm in greatest diameter, had a history of previous immunosuppressive or immunomodulatory therapy (including interferon) or had any condition associated with immunodeficiency. In addition, patients were excluded if they had any evidence of malignant neoplastic disease (except carcinoma-in-situ of the cervix or localized basal cell carcinoma), had an acute sexually transmitted disease, were

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pregnant, lactating or not practising an adequate form of contraception or had any other severe illness.

Study design

This was a multi-centre, randomised, double-blind, parallel group study to assess the efficacy of IFN alpha-2a + podophyllin combination therapy compared with placebo plus podophyllin in patients with primary condylomata acuminata. Patients were randomised to one of two treatment groups. In the IFN-treated group patients received 3 mU of IFN subcutaneously three times weekly for one week (week 0) followed by six weeks treatment with twice weekly IFN (3 mU) in combination with podophyllin 25% W/V (weeks 1–6). In the placebo group patients received matching placebo injections in the same schedule in combination with podophyllin. Podophyllin was prepared daily by the addition of 30 ml of methylated spirit to 7.5 g of podophyllin resin supplied from a central source. The podophyllin was for general use amongst trial patients rather than being provided in individual numbered patient-specific packs. Standardisation for podophyllotoxin content was not undertaken. New warts appearing during weeks 1–6 were also treated with podophyllin. Podophyllin treatment was discontinued in patients showing a complete response before week 6. IFN/placebo injections were continued until the end of week 6 regardless of response. No treatment was to be given to non or partial responders between the last treatment in week 6 and an assessment at week 10. Those patients with a complete response at week 10 were reassessed at week 26. Patients failing to show a complete response at the week 10 assessment were withdrawn and were treated with whatever therapy the investigator believed to be the most suitable. Patients who had demonstrated a complete response but noted a recurrence between ending treatment and the week 10 assessment were asked to report to the trial centre immediately where the week 10 assessment was carried out. Similarly patients noting a recurrence between weeks 10 and 26 were asked to report immediately and the week 26 assessment was performed. In each case subsequent treatment was at the discretion of the supervising physician.

Assessment schedule

A pre-study screen to include documentation of demography and duration of warts, confirmation of eligibility for study entry and

necessary haematological and biochemical investigations was completed within two weeks of commencement of study treatment.

A baseline assessment was performed immediately before the first administration of IFN/placebo in week 0 to include a description of lesion morphology (isolated, confluent or both) and document the number and distribution of lesions. A representative biopsy was taken for histology and HPV typing.

Weekly assessments were performed immediately prior to the second administration of IFN/placebo and podophyllin during weeks 1–6 to document the lesion count and disease status as defined in table 1.

A week 10 assessment of lesion count and disease status was performed in all patients. A week 26 assessment of disease status was performed for all patients demonstrating a complete response at week 10. In each case if a recurrence had occurred, a biopsy was taken and an HIV test performed.

At each assessment the nature, duration, severity and relation to treatment of any adverse events were recorded and any treatments given documented.

Laboratory investigations

Blood was taken for haemoglobin concentration, white blood cell count, platelet count, creatinine and AST during the pre-study screen, at the end of week 6 and at the week 10 assessment. In the event of unexplained or unexpected test value abnormalities, the tests were repeated immediately and followed up until the results returned to the normal range and/or an adequate explanation of the abnormality was found.

Withdrawal criteria

Criteria for patient withdrawal included pregnancy, missing one or more of the pretreatment injections, missing one week's combination treatment, progressive disease, which in the investigator's opinion required alternative treatment, deliberate or accidental breaking of the treatment code, any adverse event severe enough, in the investigator's opinion, to warrant discontinuation of treatment, loss of patient to follow-up or at the request of the patient.

Statistical analysis

Sample size was calculated to detect a 30% difference in response rates between placebo and IFN treated groups with 80% power using a two-sided test at the 5% level of significance. The primary efficacy analysis was an evaluation of the week 10 assessment of disease and was compared between treatments using logistic regression methods. The secondary efficacy analysis comprised logistic regression of the week 26 data, namely recurrence or not.

Results

In total, 124 patients were recruited at six centres. Sixty-one patients were randomised to receive IFN plus podophyllin (IFN group)

Table 1 Assessment of disease

1 = Complete response: complete disappearance of all visible lesions.
2 = Partial response: disappearance of at least 50% of lesions or reduction of at least 50% in total lesion size and no new lesions.
3 = No change: no change in number and size of lesions and no new lesions.
4 = Progression: appearance of new lesions and/or increase of at least 50% in size of existing lesions in the absence of a perilesional inflammatory reaction.
5 = Recurrence: reappearance of lesions after a complete response on the same or a new site.

Table 2 Description of Lesions on Entry

	IFN A + Podophyllin	Placebo + Podophyllin	Overall
Number of patients	61	63	124
Duration of genital warts (weeks)			
Mean (SD)	6.8 (4.9)	7.0 (5.1)	6.9 (5.0)
Median	6	6	6
Minimum	1	1	1
Maximum	24	20	24
n	61	63	124
Number of lesions			
Mean (SD)	14.2 (12.6)	19.7 (18.6)	17.0 (16.1)
Median	10.0	14.0	11.5
Minimum	1	2	1
Maximum	60	99	99
n	61	63	124
Type of lesions			
Isolated	26 (43%)	18 (29%)	44 (35%)
Confluent	9 (15%)	15 (24%)	24 (19%)
Both	26 (43%)	30 (48%)	56 (45%)
Internal lesions			
Present	8 (13%)	14 (22%)	22 (18%)
Not present	53 (87%)	49 (78%)	102 (82%)

and 63 to receive placebo plus podophyllin (placebo group).

Demographic data and prestudy characteristics

There were no significant differences between the treatment groups in age, weight, height, race or sexual orientation. There was a significantly higher proportion of males in the IFN-treated group (35 males (57%)) compared with the placebo group (22 males (35%)). The groups were comparable for concomitant signs/symptoms or diseases and concomitant medication on study entry. Table 2 summarises a description of the lesions on entry. The placebo group had a slightly greater median number of lesions, fewer isolated and more confluent lesions and slightly more internal lesions than the IFN group. Disease duration was similar. In all subsequent formal statistical analysis the imbalance in sex ratio and prestudy lesion characteristics were accounted for before treatments were compared.

Histopathology and HPV typing data

In total 144 biopsies were performed, 121 on initial assessment and 23 in cases of recurrent warts. Of the initial biopsies 62 were in the placebo group and 59 in the IFN group. The morphology of the lesions in the placebo

group was classified as flat wart in 44 (71%), papillary or exophytic in 14 (22.6%), inverted or endophytic in 2 (3.2%) and unclassified in 2 (3.2%). The morphology in the IFN group was classified as flat wart in 43 (72.9%), papillary or exophytic in 10 (16.9%), inverted or endophytic in 4 (6.8%) and unclassified in 2 (3.4%). Koilocytosis was present in 34 (54.8%) of the placebo group biopsies and 40 (67.8%) of IFN group biopsies. One biopsy in the placebo group showed low grade dysplasia while low grade dysplasia was detected in 6 cases and high grade dysplasia in 1 case in the IFN group. HPV typing was performed using in situ hybridization techniques. HPV types 6 and 11 were detected in 16 (25.8%) of placebo group biopsies and 23 (40%) of IFN group biopsies. HPV types 16 and 18 were detected in two cases in each group. No cases were positive for HPV 31.

Of repeat biopsies nine occurred in the placebo group and 14 in the IFN group. The morphology, degree of dysplasia, presence or absence of koilocytosis and HPV typing were comparable.

Efficacy analysis

Analysis populations were defined as follows: *Safety Population* comprised all patients who received any of their trial medication. Further analysis populations were defined having considered visit discipline and specified "visit windows" for valid assessment data collection. Before defining the *The Intent to Treat Population* and the *Efficacy Population*, two types of visit data were excluded—those visits which fell outside all visit windows, and one of the visits when two visits occurred within the same window. The analysis for the *Efficacy Population* was performed using all remaining patient data, excluding that regarded as being in violation of the study protocol. The analysis for the *Intent to Treat Population* was performed using all remaining patient data, with all missing data being replaced by the last observation, that is, a last observation carried forward analysis.

The primary efficacy analysis was an evaluation of the week 10 assessment of disease (table 3). As the scale used for this measurement was not strictly ordinal, it was dichotomised into complete response or not. In addition, since 84 patients were recruited in Belfast with considerably smaller numbers in each of the other five centres any effect on response due to centre was analysed by comparing data from Belfast with those from the other centres pooled. There was no statistically significant effect on complete response rate due to centre, duration of disease, sex or number of lesions at entry in either the Intent to Treat Population (table 4) or the Efficacy Population (table 5). Having adjusted for the above effects there was no significant difference between IFN and placebo treated groups in complete response rates at week 10 either for the Intent to Treat Population or the Efficacy Population with odds ratios of 1.12 ($p = 0.80$) and 1.55 ($p = 0.39$) respectively (tables 4 and 5).

Table 3 Assessment of Disease at Week 10

	IFN A + Podophyllin	Placebo + Podophyllin	Overall
<i>(Intent to Treat Population)</i>			
Number of Patients	61	63	124
Complete response	19 (32%)	17 (28%)	36 (30%)
Partial response	14 (24%)	23 (38%)	37 (31%)
No change	2 (3%)	8 (13%)	10 (8%)
Progression	12 (20%)	9 (15%)	21 (18%)
Recurrence	12 (20%)	4 (7%)	16 (13%)
Total	59 (100%)	61 (100%)	120 (100%)
<i>(Efficacy Population)</i>			
Number of Patients	59	59	118
Complete response	15 (36%)	11 (26%)	26 (31%)
Partial response	12 (29%)	16 (37%)	28 (33%)
No change	1 (2%)	4 (9%)	5 (6%)
Progression	6 (14%)	8 (19%)	14 (16%)
Recurrence	8 (19%)	4 (9%)	12 (14%)
Total	42 (100%)	43 (100%)	85 (100%)

Table 4 Week 10—Assessment of Disease: Intent to Treat Population

Effect	Odds Ratio	95% Confidence Interval	p value
Centre* (Belfast ÷ Others)	0.61	0.26 to 1.43	0.25
Disease duration	1.03	0.95 to 1.11	0.52
Sex (Male ÷ Female)	0.72	0.30 to 1.75	0.47
Number of lesions on entry	0.98	0.95 to 1.02	0.40
Type of lesion: isolated (Yes ÷ No)	1.02	0.31 to 3.36	0.98
Type of lesion: confluent (Yes ÷ No)	0.59	0.21 to 1.67	0.32
Internal lesions (present ÷ not present)	0.65	0.18 to 2.29	0.50
Treatment† (IFN ÷ placebo)	1.12	0.48 to 2.62	0.80

*Test for a treatment-by-centre interaction: $p = 0.92$.

†Adjusted for the other effects listed

Table 5 Week 10—Assessment of Disease: Efficacy Population

Efficacy	Odds Ratio	95% Confidence Interval	p value
Centre* (Belfast ÷ others)	0.97	0.30 to 3.10	0.96
Disease duration	0.98	0.89 to 1.08	0.70
Sex (male ÷ female)	0.71	0.24 to 2.08	0.53
Number of lesions on entry	0.98	0.94 to 1.03	0.48
Type of lesion: isolated (yes ÷ no)	0.64	0.16 to 2.56	0.53
Type of lesion: confluent (yes ÷ no)	0.35	0.09 to 1.27	0.11
Internal lesions (present ÷ not present)	1.19	0.24 to 6.06	0.83
Treatment† (IFN-A ÷ placebo)	1.55	0.57 to 4.22	0.39

*Test for a treatment-by-centre interaction: $p = 0.5$.

†Adjusted for the other effects listed

Twenty-nine patients (14 IFN group, 15 placebo group) who were complete responders at week 10 were successfully followed-up for week 26 assessment, with 20 patients (8 on IFN, 12 on placebo) still demonstrating a complete response (table 6). The sex of patients demonstrating persistence of complete response was seven female and one male in the IFN-treated group and 10 female and two male in the placebo-treated group. Recurrence was noted in one female and five males in the IFN group and two males in the placebo group. Female patients showed a significantly improved response compared with males with an odds ratio of 0.03 ($p = 0.04$). Allowing for the above effect there was no significant difference between IFN and placebo treated groups in recurrence rate at week 26 with an odds ratio of 0.17 ($p = 0.36$) (table 7).

Caution, however, must be exercised in interpreting the results of analysis of week 26 data as it was based on a non-randomised and

biased subset of the population and was only undertaken for those patients in the safety population who provided week 26 data.

Safety analysis

In total 58 adverse events were reported by 35 patients (28%) with 21 patients (34%) on IFN reporting 34 events and 14 patients (22%) on placebo reporting 24 events. Of the 58 events, 32 were mild, 21 moderate and 5 severe with 26 regarded as probably related to study drug, 14 possibly related, seven remotely related, 10 not related and one not assessable. The only events reported by more than three patients were application site reaction reported by 12 patients (eight on IFN, four on placebo) and malaise reported by 12 patients (10 on IFN, two on placebo). Clearly placebo fared better compared with IFN-treated patients.

Laboratory data

All HIV antibody tests were negative. Measurements of haemoglobin, platelets, AST and creatinine were within the reference range in at least 90% of patients in each treatment group and overall at weeks 0, 6 and 10. For leucocytes the corresponding figure was 79% with the IFN-treated group showing a greater tendency to results outside the reference range, although no such results were clinically significant.

Discussion

Interferons possess antiviral, antiproliferative and immunomodulatory effects and as a result have been proposed as potential therapeutic agents for anogenital HPV infection. Because of both the multicentric nature of genital HPV infection and its ability to produce latent and clinically inapparent "disease" the systemic route of administration would appear particularly appropriate. Review of the literature reveals somewhat conflicting findings on the efficacy of IFN monotherapy with comparison between studies being difficult because of variations in study design, IFN subtype, route of administration, nature of warts treated and endpoint measures of efficacy chosen. Several early studies showed some degree of clinical efficacy by parenteral and intralesional routes of administration in both primary and recalcitrant lesions.²⁻⁸ Several of these studies, however, involved relatively small numbers of patients, were open label and uncontrolled. The IFN subtype, nevertheless, did not appear to determine the degree of clinical response.^{4,8,9} There are few trials directly comparing IFN monotherapy with a standard first line therapeutic agent. In one notable trial comparing systemic IFN alpha-2a with podophyllin treatment for primary anogenital condylomata systemic IFN was significantly less effective.¹⁰ It is generally accepted that IFN monotherapy is not superior to currently available standard therapeutic techniques which are usually simpler and cheaper to administer.⁸ By combining a standard chemical or physical "debulking" therapy for clinically

Table 6 Week 26—Assessment of Disease: Safety Population

	IFN + Podophyllin	Placebo + Podophyllin	Overall
Number of Patients	14	15	29
Complete response	8 (57%)	12 (80%)	20 (69%)
Recurrence	6 (43%)	2 (13%)	8 (28%)
Lost to follow-up	0 (0%)	1 (7%)	1 (3%)
Total	14 (100%)	15 (100%)	29 (100%)

Table 7 Week 26—Assessment of Disease: Safety Population

Effect	Odds Ratio	95% Confidence Interval	p value
Centre* (Belfast ÷ others)	Not possible to assess the centre effect		
Disease duration	1.00	0.75 to 1.35	0.98
Sex (male ÷ female)	0.03	0.001 to 0.87	0.04
Number of lesions on entry	1.41	0.85 to 2.35	0.19
Type of lesion: isolated (yes ÷ no)	0.14	0.0001 to 158.45	0.59
Type of lesion: confluent (yes ÷ no)	0.04	0.0001 to 12.86	0.27
Internal lesions (present ÷ not present)	Not possible to assess the effect of internal lesions		
Treatment† (IFN-A ÷ placebo)	0.17	0.004 to 7.32	0.36

*Test for a treatment-by-centre interaction: Not possible to test for this.

†Adjusted for the other effects listed

overt disease with adjunctive systemic IFN it was hoped that both primary clinical response and recurrence rates would improve. As podophyllin is one of the most commonly used first line treatments for anogenital warts and is frequently administered on a twice weekly basis it was decided to evaluate a twice weekly combination therapy regime with one week pre-treatment with IFN to "presensitize" lesions.

The primary parameter of efficacy was complete response rate at week 10 which occurred in 32% and 36% of IFN-treated patients in the *Intent to Treat* and *Efficacy Populations* respectively with 28% and 26% of placebo-treated patients showing a similar response. There was no significant difference between the IFN and placebo-treated groups. Although disappointingly low, the complete response rate in this study is within the range of 22–71% reported in previous studies with podophyllin treatment.^{11–13} A further factor to consider when evaluating the complete response rate is that this assessment of disease status occurred at week 10, at least four weeks after the last application of podophyllin. As a consequence, some patients who had shown an initial complete response developed recurrent disease during this period and were classified as recurrent disease cases rather than complete responders. In contrast to our own findings in a study by Douglas *et al* intralesional IFN-alpha 2b combined with podophyllin was compared with podophyllin treatment alone in a single blind combination trial in patients with primary or recurrent/recalcitrant warts with an overall improvement in complete response rate in the combined therapy group.¹⁴ There are in addition reports of improved efficacy of adjuvant systemic IFN in conjunction with ablative therapy of various kinds in patients with recalcitrant anogenital warts.^{15–17} Once again these studies have methodological limitations in terms of patient numbers, limited controls and duration of follow-up. A recent large placebo-controlled double-blind combined therapy with laser surgery and systemic IFN alpha-2a with a follow-up period of 36 weeks showed no beneficial effects of adjuvant IFN in terms of complete response or recurrence.¹⁸ A similar conclusion was reached in a trial comparing systemic IFN alpha-2a combined with cryotherapy versus cryotherapy alone.¹⁹

The histopathology and HPV DNA positivity findings in this study are somewhat atypical with a predominance of morphologically flat lesions and an overall HPV DNA positivity rate of approximately 35 per cent. This is in contrast to other studies demonstrating the more usual predominance of papillary or exophytic morphology and HPV DNA positivity rates of 70% to 80%.^{10,18} The reasons for such differences are not immediately clear but may involve a lower sensitivity of in situ hybridisation techniques compared with polymerase chain reaction techniques. These atypical features may be of relevance in evaluating the relatively low overall complete response rate.

Statistical analysis of our week 26 data must be viewed with caution because of the previously described bias but suggested no significant benefit of adjunctive IFN therapy on recurrence rates. Analysis of pre-treatment characteristics predictive of clinical outcome at week 10 showed no significant effect on complete response of duration of disease, sex, number of lesions, type of lesions or the presence of internal lesions in keeping with previous reports.¹⁸ Several studies have, however, shown a poorer response with longer duration of disease,¹⁴ male sex^{10,14} and with large numbers of lesions.^{10,15,19}

In summary we conclude that at the dose and with the regime described combination therapy with systemic IFN alpha-2a and podophyllin is no more efficacious than podophyllin alone in terms of complete response or recurrence in patients with primary anogenital condylomata acuminata.

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